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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,331	04/22/2005	Birgit Bollbuck	PA/4-32743A	1761
75074 7590 03/24/2008 NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC. 400 TECHNOLOGY SQUARE CAMBRIDGE, MA 02139				
EXAMINER SACKEY, EBENEZER O				
ART UNIT		PAPER NUMBER		
1624				
MAIL DATE		DELIVERY MODE		
03/24/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/532,331

Applicant(s)

BOLBUCK ET AL.

Examiner

EBENEZER SACKEY

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6 and 9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-893)
Paper No(s)/Mail Date 04/22/05.

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims

Claims 1-30 are pending.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Information Disclosure Statement

Receipt of the Information Disclosure Statement filed on 04/22/05 is acknowledged and has been entered into the file. A signed copy of the 1449 is attached herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The use of the term "comprising" consistently in compound claims renders the claims indefinite because comprising is an open-ended word, which permits the inclusion of unrecited elements. The use of the term comprising to introduce claimed structure means that the ingredients covered by these claims may involve more elements than those positively recited. Ex parte Gottzein et al., 168 U.S.P.Q. 176 (PTO Bd. App. 1969). Also see Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO Bd. App. 1948).

2. The use of capital letters in the claims render the claims ambiguous since no period is permitted anywhere in the claims except the end of the claims. Correction is required.

3. Claims 2 and 4 are replete with multiple sentences. Claims cannot contain more than one sentence and the period should appear at the end of the sentence. See M.P.E.P. 608.01(m).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject

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matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

- 1) Nature of invention.
- 2) State of prior art.
- 3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure
- 4) Level of predictability in the art.
- 5) Amount of direction and guidance provided by the inventor.
- 6) Existence of working examples.
- 7) Breadth of claims.
- 8) Level of ordinary skill in the art.

See below:

Applicants are claiming a composition for inhibiting chemokine receptors (CCR1), or reducing inflammation comprising the administration of compounds of formula (I). The claims are not enabling for any specific disease. Thus, the various diseases are being rejected for the reasons below.

1) Nature of the invention.

The nature of the invention is the treatment of various disease states by selective inhibition of CCR1 receptor. As stated above however, claim 6 recites the treatment of diseases with various pathways and mechanisms with no correlation to each other.

2) State of the prior art and the predictability or lack thereof in the art.

The prior art teaches screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease or what diseases are covered). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instantly claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between the inhibition of CCR1 and the various diseases claimed as capable of being treated by compounds of formula (I), one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the various diseases.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of disease to be treated, and then determine which of the thousands of compounds would be suitable for said treatment because the dosage regimen for influenza (a viral disease) cannot possibly be the same for chronic and acute organ rejection (relating to the immune system).

4) Level of predictability in the art.

The art pertaining to the treatment of any disease condition remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art.

Firstly, for a compound or genus to be effective against all inflammatory diseases is contrary to medical science. "Inflammation" for example, is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for diseases associated with inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against all inflammation related diseases generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is

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infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found on page 25 wherein *in vitro* activity (chemotaxis assay) is provided. However, that embraces a myriad of conditions. In addition, the gap between *in vitro* activity and *in vivo* utility is large enough to warrant thorough and compelling clinical data.

6) Existence of working examples.

As discussed above, working example is found on page 148-152 wherein *in vitro* activity is provided. Applicant's limited working example does not enable one of ordinary skill in the art to treat the numerous amounts of diseases encompassed by the instant invention.

7) Breadth of claims.

Diseases recited on page 151-152 are extremely varied due to the various pathways and mechanisms involved.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of the various diseases listed. Thus, necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

Genentec Inc. V. Novo Nordisk A/S (CAFC) 42 USPQ 2D 1001, states that:

“a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors, and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in instant claims, with no assurance of success.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for the various diseases. It

establishes that it is not reasonable to any agent to be able to treat all of the various diseases generally.

This rejection can be overcome by reciting specific closely related diseases.

Claim Rejections - 35 USC § 102

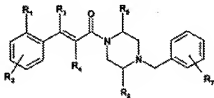
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by
Blumberg et al., (U.S. Patent number 7,098,212).

Applicants claim compounds of structural formula (I), wherein all the substituents



are as defined in the claims:

Blumberg et al., disclose a series of compounds which anticipate the current claims. See for example column 48, compound 1-[4-(4-Fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-3-(2-hydroxy-4-methylphenyl)propan-1-one. Blumberg et al., anticipate the instant compound when R₇ is fluorine, each of R₅ and R₆ is methyl, R₁ is X-R₁₀, where X is O and R₁₀ is hydrogen and R₂ is methyl.

The reference is replete with anticipatory compounds. See Example 10, Example 11, lines 34-35, Example 25. Note the current application has a provisional

application date of October 22, 2001.

Claim Rejections - 35 USC § 102

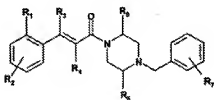
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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

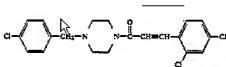
Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohtaka et al., (U.S. Patent number 4,742,062).

Applicants claim compounds of structural formula (I), wherein all the substituents



are as defined in the claims:

Ohtaka et al. disclose compounds which anticipate the claims above when R₇ is chlorine, each of R₅ and R₆ is hydrogen, each of R₃ and R₄ is hydrogen and each of R₁



and R_2 is chlorine:

. See column 3, process C.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Sackey whose telephone number is (571) 272-0704. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

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supervisor, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

EOS

**/James O. Wilson/
Supervisory Patent Examiner
Art Unit 1624**